Attorney Docket No.: 5753.204-US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Nielsen et al. Confirmation No: 7015

Serial No.: 09/831,656 Group Art Unit: 1638

Filed: May 11, 2001 Examiner: Kallis, Russell

For: Transgenic Plant Expressing Maltogenic Alpha-Amylase

CERTIFICATE OF MAILING UNDER 37 CFR 1.8(a)

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I hereby certify that the attached correspondence comprising:

1. Transmitttal of Appeal Brief (in duplicate)
2. Brief on Appeal and a copy of pending claims (in triplicate)

is being deposited with the United States Postal Service as first class mail in an envelope addressed to the address indicated above on July 22, 2004.

Julie Tabarovsky

Julie Tabarovsky
(signature of person mailing paper)

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TRANSMITTAL OF APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith in triplicate is an Appeal Brief in this application with respect to the Notice of Appeal filed May 3, 2004. The required fee for submitting an appeal brief is estimated to be $330.

Applicant hereby petitions for an extension of time under 37 CFR 1.136 for one month. If an additional extension of time is required, please consider this a petition therefor. The required extension fee is estimated to be $110.

Please charge the required extension and appeal fees, estimated to be $440, to Novozymes North America, Inc., Deposit Account No. 50-1701. A duplicate of this sheet is enclosed.

Respectfully submitted,

Date: July 22, 2004

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Attorney Docket No.: 5[illegible]53.204-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby appeal from the final rejection of claims 23-25 and 27-37, all the claims pending in the present application.

I. REAL PARTY IN INTEREST

The name of the real party in interest in this appeal is Novozymes A/S.

II. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences relating to the instant application.

III. STATUS OF THE CLAIMS

Claims 1-22 and 26 have been cancelled. Claims 23-25 and 27-37 remain pending in the application. Claims 38-42 are withdrawn as a result of the restriction requirement and Applicants' election of Group I. All pending claims (copy attached), are included in this appeal.

IV. STATUS OF AMENDMENTS

The amendment filed under 37 C.F.R. § 1.116 on May 3, 2004 has been entered. The amendment was stated to overcome the 35 U.S.C. 103(a) obviousness rejection. However, the 35 U.S.C. 112 written description and enablement rejections were maintained.

V. SUMMARY OF THE INVENTION

The claimed invention relates to transgenic cereal plant cells (claims 23-25 and 27-29), transgenic cereal plants (claims 30-34), and transgenic cereal plant seeds (claims 34-37) which have been transformed with a nucleic acid sequence encoding a maltogenic alpha-amylase. See the specification at page 2, lines 1-21.

A "maltogenic alpha-amylase" is the common name for enzymes which are generally classified in EC 3.2.1.133. See the specification at page 2, line 25-26. A maltogenic alpha-amylase has a primary enzymatic activity which results in the hydrolysis of amylopectin and amylose to maltose and longer maltodextrins. See the specification at page 2, lines 25-32. A "maltogenic alpha-amylase" should be distinguished from the enzymes referred to as "alpha-amylases." "Alpha-amylases", which are generally classified in EC 3.2.1.1, have very different enzymatic activity than the "maltogenic alpha-amylases" involved in the present invention. Compare, e.g., (EC 3.2.1.133) to (E.C. 3.2.1.1.), provided as Exhibits in the Amendment and Response of May 3, 2004.

The specification discloses how to prepare transgenic cereal plant cells, cereal plant seeds and cereal plants comprising a nucleic acid encoding a maltogenic alpha-amylase by cloning a nucleic acid sequence encoding a maltogenic alpha-amylase (page 12, line 30 to page 14, line 6), preparing an expression construct containing the nucleic acid sequence (page 14 to page 16, line 7 and Example 1 and 2) and transforming plant cells with the gene encoding a maltogenic alpha-amylase to prepare transgenic cereal plant cells, cereal plant seeds and cereal plants (page 16, line 25 to page 17, line 35 and Example 1). The specification also discloses how to regenerate a transgenic cereal plant from plant cells, in particular, protoplasts, which have been transformed with the gene encoding a maltogenic alpha-amylase. See Example 2.

The specification further discloses that any nucleic acid encoding a maltogenic alpha-amylase may be used in preparing the transgenic cells, seeds and plants. See the specification at page 2, lines 1-17. The independent claims, however, currently recite that the nucleic acid encodes a maltogenic alpha-amylase having an amino acid sequence which has at least 70% identity to amino acids 34-719 of SEQ ID NO:2. SEQ ID NO:2 is the amino acid sequence of the maltogenic alpha-amylase encoded by the nucleic acid sequence shown in SEQ ID NO:1, which is contained in *Bacillus* strain NCIB 11837 and which is deposited in strain DSM 11837. See the specification at page 2, line 34 to page 3, line 15 and the Sequence Listing.

In addition to the maltogenic alpha-amylase of SEQ ID NO:2, numerous other maltogenic alpha-amylases are disclosed in the specification. See the specification at page 4 to page 10. These maltogenic alpha-amylases are also described in WO 99/43794, which corresponds to

issued U.S. Patent No. 6,162,628, and which is referenced in the specification at page 3, line 12, at page 6, lines 11 and 15.

Maltogenic alpha-amylases have beneficial properties as anti-staling agents in preparing baked goods. See the specification at page 3, lines 21-35. The transgenic cereal plant cells, cereal plant seeds and cereal plants of the present invention can be used, among other things, to prepare wheat flour for use in preparing baked goods. See, e.g. the specification at page 18, line 20 to page 19, line 9 and Examples 3, 4 and 5. In particular, the maltogenic alpha-amylase produced by the transgenic cereal plant seeds can be used to retard the staling properties of the baked goods when baked goods are made from such transgenic cereal plant seeds. See the specification at page 19, lines 4-9 and Example 5.

The specification further discloses that unlike alpha-amylases, which must be dosed very carefully in tight intervals in baking applications to avoid gummy, non-elastic sticky crumb of the baked good, maltogenic alpha-amylases have a very broad dosage range. See the specification at page 3, lines 20-35, and page 19, lines 11-24. While this property of maltogenic alpha-amylases make maltogenic alpha-amylases very suitable for baking, the inventors have also determined that it provides an advantage for their transgenic expression in seeds. See the specification at page 3, line 35 to page 4, line 4.

VI. ISSUES

The outstanding issues are:

(1) Whether the specification provides adequate written description support for claims 23-25 and 27-37;

(2) Whether claims 23-25 and 27-37 are enabled;

VII. GROUPING OF CLAIMS

For purposes of determining patentability, the claims do not stand or fall together.

Claim 23 recites a transgenic cereal plant cell comprising a nucleic acid encoding a maltogenic alpha-amylase which has an amino acid sequence which has at least 70% identity to amino acids 34-719 of SEQ ID NO:2.

Claim 25 does not stand or fall with claim 23 because claim 25 specifically recites that the maltogenic alpha-amylase "has the amino acid sequence of amino acids 34-719 of SEQ ID NO:2." As applicants explained in the submitted amendments, the scope of claim 25 corresponds precisely to the subject matter the Examiner has acknowledged Applicants have adequately described and enabled in the specification. For example, see the Examiner's

statements in the Office action of April 11, 2003 at page 3 ("Applicant does not describe any DNA or amino acid sequence other than SEQ ID NO:1 and 2 or plant cells and plants transformed therewith.") page 4 ("Applicant teaches SEQ ID NO:1 and 2...."). Applicants requested that the Examiner withdraw the 35 U.S.C. 112 rejections as applied to claim 25 given that the rejection of this claim directly contradicts the statements the Examiner has made in the Official actions. The Examiner has never agreed to this request and has maintained the rejection of claim 25.

Claim 29 does not stand or fall with claim 23 because claim 29 specifically recites that the nucleotide sequence encoding the maltogenic alpha-amylase is derived form Bacillus strain NCIB 11837. This sequence has been deposited as strain DSM 11837. A deposit of a gene provides both adequate written description and enablement for using that gene in preparing the claimed transgenic cells, seeds and plants.

Claim 31 recites a transgenic cereal plant comprising a nucleic acid encoding a maltogenic alpha-amylase which has an amino acid sequence which has at least 70% identity to amino acids 34-719 of SEQ ID NO:2.

Claim 33 does not stand or fall with claim 31 because claim 33 specifically recites that the maltogenic alpha-amylase "has the amino acid sequence of amino acids 34-719 of SEQ ID NO:2." The scope of claim 33 corresponds precisely to the subject matter the Examiner has acknowledged Applicants have adequately described and enabled in the specification. See the Examiner's statements in the Office action of April 11, 2003 at page 3 ("Applicant does not describe any DNA or amino acid sequence other than SEQ ID NO:1 and 2 or plant cells and plants transformed therewith.") page 4 ("Applicant teaches SEQ ID NO:1 and 2....").

Claim 35 recites a transgenic cereal seed comprising a nucleic acid encoding a maltogenic alpha-amylase which has an amino acid sequence which has at least 70% identity to amino acids 34-719 of SEQ ID NO:2.

Claim 36 does not stand or fall with claim 35 because claim 36 specifically recites that the maltogenic alpha-amylase "has the amino acid sequence of amino acids 34-719 of SEQ ID NO:2." The scope of claim 36 corresponds precisely to the subject matter the Examiner has acknowledged Applicants have adequately described and enabled. See the Examiner's statements in the Office action of April 11, 2003 at page 3 ("Applicant does not describe any DNA or amino acid sequence other than SEQ ID NO:1 and 2 or plant cells and plants transformed therewith.") page 4 ("Applicant teaches SEQ ID NO:1 and 2....");

VIII. ARGUMENTS

A. The Specification Provides Written Description Support For Claims 23-25 and 27-37

1. The Written Description Rejection

Claims 23-25 and 27-37 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly lacking adequate written description support. The written description rejection initially focused on both the genus of nucleic acids encoding maltogenic alpha-amylases and the sub-genus of nucleic acids encoding maltogenic alpha-amylases having 70% sequence identity to SEQ ID NO:2. Although Applicants maintain that the genus of maltogenic alpha-amylases is adequately described in the specification, to expedite prosecution, the claims were amended during prosecution to recite that the "nucleotide sequence encodes a maltogenic alpha-amylase having at least 70% identity to amino acids 34-719 of SEQ ID NO:2."

The Examiner alleges that Applicants have not described or exemplified the genus of the recitation of nucleic acids encoding maltogenic alpha-amylases that can be used in preparing in the claimed transgenic cereal plant cells, cereal plant seeds and cereal plants. In particular, the Examiner alleges that Applicants have only described and exemplified one nucleic acid sequence (SEQ ID NO:1) encoding one maltogenic alpha-amylase (SEQ ID NO:2).[1] See the Office action of April 11, 2003 at page 3-7. The Examiner alleges that "Applicant does not describe any DNA or amino acid sequences other than SEQ ID NO:1 and 2 or a plant cells and plants transformed therewith." See the Office action of April 11, 2003 at page 3.

In the response of August 19, 2003, Applicants pointed out that both the specification and the patent publication referenced in the specification (WO 99/43794 which corresponds to U.S. Patent No. 6,162,628), disclose numerous maltogenic alpha-amylases, which are representative of the claimed genus, and this clearly shows that Applicants were in possession of numerous nucleic acids encoding maltogenic alpha-amylases. Applicants also questioned how claim 25, which further limits the claims by reciting specifically that the nucleic acid is the

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1 Although the Examiner acknowledges that Applicant have exemplified a nucleic acid encoding the maltogenic alpha-amylase of SEQ ID NO:2, the Examiner has included claims 25, 29, 33 and 36 in the written description and enablement rejections even though these claims are specifically limited to either a nucleic acid sequence encoding the maltogenic alpha-amylase of SEQ ID NO:2 or to a maltogenic alpha-amylase obtained from a specific microorganism (Bacillus strain NCIP 11837). Applicants initially believed this was an obvious mistake and pointed the contradiction out to the Examiner. However, the Examiner has never withdrawn the written description and enablement rejections as applied to these claims. Applicants do not believe the Examiner can properly maintain such rejections given his own admissions as to what is disclosed.

nucleic acid sequence encoding a maltogenic alpha-amylase of SEQ ID NO:2 could possibly be included in the Examiner's written description rejection given that it corresponded to exactly what the Examiner admitted was described in the specification.

In the Final Office action of October 29, 2003, the Examiner dismissed the representative species of maltogenic alpha-amylases disclosed in both the specification and in WO 99/43794 (referred to as the '628 patent in the Office actions and amendments) as showing proteins not nucleic acids, whereas the claims require description of nucleic acids. In particular, the Examiner stated that "the '628 patent deals with proteins while the claims of instant Application are drawn to the genes encoding proteins." See page 4 of the Final Office action. The Examiner also alleged that the '628 Patent does not provide conserved sequences of the genes which are correlated with function, as per MPEP 2163 and Written Description Guidelines." *See id.* The Examiner further alleged that "Applicant has not described the claimed sequences of the invention as argued..., Applicant has not taught how to make the broadly claimed sequences of the invention and the host cells and plants therewith." See id. The Examiner did not respond to Applicants request to withdraw the rejection of claim 25 on the basis it contradicted the Examiner's own statements of what has been described.

In response to the Final Office action, Applicants expedited prosecution by amending the claims to recite that the "nucleotide sequence encodes a maltogenic alpha-amylase having at least 70% identity to amino acids 34-719 of SEQ ID NO:2." This limitation was found in the dependent claims. Applicants also argued that the maltogenic alpha-amylases described in the specification evidence possession of numerous maltogenic alpha-amylase sequences for practicing the claimed invention and that a description of the proteins was sufficient for the artisan to conclude that Applicants were also in possession of nucleic acids encoding such proteins. Applicants also submitted a declaration from one of the inventors of the cited patent publication WO 99/43794, who attests to the facts of the preparation of the maltogenic alpha-amylases and possession of nucleic acids encoding the maltogenic alpha-amylase variants. In particular, Dr. Cherry stated that the disclosure of an amino acid sequence is sufficient to place the artisan in possession of the nucleic acid sequence encoding the amino acid sequence as such skills are routine in the art. Dr. Cherry also stated that contrary to the Examiner's statements in the Office Actions, the specification of present application and WO 99/43794 (i.e., the '628 patent) describe functional maltogenic alpha-amylase which can be confirmed by carrying out the assays described in WO 99/43794.

In the Advisory Action, the Examiner concludes that the written description rejection is maintained because Applicants have not provided guidance as to which combinations of the "vast myriad of amino acid substitutions cited in the specification would recover maltogenic alpha-amylase activity over the entire claimed scope of 70% sequence identity to amino acid residues 34-719 of SEQ ID NO:2." The Examiner also dismisses the Declaration of Dr. Joel Cherry as his "opinion" which does not rebut the evidence provided by the Examiner.

2. The Legal Standard

The written description requirement of 35 U.S.C. 112, first paragraph, is fulfilled when the patent specification describes the claimed invention in sufficient detail such the claim limitations are described so that one of skill in the art would recognize that the applicants had invented the subject matter. *See Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991), *In re Herschler*, 591. F.2d 693, 700 (CCPA 1979). The written description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

The written description requirement can be met by showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with know or disclosed correlation between function and structure, or some combination of such characteristics. See, e.g., *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997); *Enzo Biochem v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). A description of a claimed genus may be achieved by recitation of a representative number of species falling within the scope of the genus or by a recitation of structural features common to the members of the genus which constitute a substantial portion of the genus. See *Eli Lilly and Co.*, 43 U.S.P.Q.2d at 1569.

The Patent Office's "Guidelines for the Examination of Patent Applications Under The 35 U.S.C. 112, ¶ 1 'Written Description' Requirement" also provide guidance as to how to determine if there is sufficient written description to inform the artisan that the applicant was in possession of the claimed genus at the time the application was filed. These guidelines reiterate the Federal Circuit's law that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by relevant identifying characteristics, i.e., structure or other physical and/or chemical characteristics, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In particular, the PTO has determined that the written

description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.,* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines for Examination of Patent Applications under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, 66 Fed.Reg. 1099, 1106 (Jan. 5, 2001). The Written Description Guidelines also state that a representative number of species requires that the species which are expressly described be representative of the entire genus. The Written Description Guidelines further state that what constitutes a representative number is an inverse function of the predictability of the art.

3. Argument

The Examiner's written description rejection primarily focuses on whether Applicants' specification provides sufficient written description support for an artisan to conclude that Applicants were in possession of the claim element of the "nucleotide sequences" which encode maltogenic alpha-amylases having at least 70% identity to amino acids 34-719 of SEQ ID NO:2 which are used to transform the claimed cereal plant cells, cereal plants and cereal plant seeds.

It is well-established in the art that the definition of a genus of genes encoding polypeptides having an enzyme activity of interest is accomplished by using structural features that show the relatedness of the genes and their encoded products which are members of the genus. For decades the scientific community has relied on the structural features of (1) percent identity of the amino acid sequences encoded by the genes; (2) percent homology of the nucleic acid sequences of the genes; and/or (3) nucleic acid hybridizations under defined stringent conditions as structural features to reasonably predict the function of polypeptides encoded by genes, and to place the genes and encoded polypeptides into an existing genus. In particular, polypeptides having a high degree of sequence similarity to another polypeptide are expected to have a very similar function. Nucleic acids having a high degree of sequence similarity to another nucleic acid are likewise expected to encode a polypeptide having a very similar function. Nucleic acids which hybridize to another nucleic acid under certain stringent conditions are also expected to encode a polypeptide having a very similar function. The United States Patent Office and patent authorities throughout the world have also accepted these structural features to define a genus of genes or proteins, as evidenced by the numerous issued patents containing these structural features.

All of the independent claims of the pending application recite the structural feature that the nucleic acid sequence used to transform the cereal plant cells, cereal plant seeds or cereal

plants is a nucleotide sequence encoding a maltogenic alpha-amylase which "has an amino acid sequence which has at least 70% identity to amino acids 34-719 of SEQ ID NO:2." The structural feature of 70% identity to a reference sequence inherently defines the function of the encoded products and provides a reasonable prediction of relatedness and the identification of members of the genus. In particular, it is accepted in the art that polypeptides having at least 70% identity to a reference polypeptide are reasonably expected to have a very similar function as the reference polypeptide as such polypeptides will only differ from the reference sequence by from 1 amino acid to 30% of the amino acids. It is also follows, and is accepted in the art, that nucleic acid sequences encoding polypeptides having 70% identity to a reference polypeptide will encode a polypeptide having a very similar function to the reference polypeptide.

In addition to structural features common to the members of the genus, the possession of the recited genus is also shown by the recitation of a representative number of species falling within the scope of the genus. The Examiner's reasoning for maintaining the written description rejection primarily relies on the conclusion that the specification discloses only one gene (SEQ ID NO:1) encoding one maltogenic alpha-amylase (SEQ ID NO:2). The Examiner's allegations are factually incorrect as the specification discloses at least hundreds of representative examples of nucleic acids encoding maltogenic alpha-amylase which have at least 70% identity to amino acids 34-719 of SEQ ID NO:2. In particular, maltogenic alpha-amylases specifically disclosed in the instant specification include the numerous variants of the maltogenic alpha-amylase of SEQ ID NO:2, as follows:

(1) A maltogenic alpha-amylase having one or more of the following positions altered in SEQ ID NO:2: D127, V129, F188, A229, Y258, V281, F284, T288, N327, M330, G370, N371, D372, L71, S72, V74, L75, L78, T80, L81, G83, T84, D85, N86, T87, G88, Y89, H90, G91, T94, R95, D96, F97, I174, S175, N176, D178, D179, R180, Y181, E182, A183, Q184, K186, N187, F188, T189, D190, A192, G193, F194, S195, L196. See the specification at page 7, lines 1-12.

(2) A maltogenic alpha-amylase having one or more of the following substitutions in SEQ ID NO:2: D127N/L, V129S/T/G/V, F188E/K/H, A229S/T/G/V, Y258E/D/K/R/F/N, V281L/T, F284K/H/D/E/Y, T288E/K/R, N327D, M330L/F/I/D/E/K, G370N, N371D/E/G/K, D372N/V, L71I, S72C, V74I, L75N/D/Q/I/V, L78N/I, T80I/L/V/S/N/G, L81I/V/S/T/N/Q/K/H, G83A/S/T/N/Q/E/D/R/H/L, T84S/A/N/D/G, D85A/T/S/N/G, N86Q/E/D/Y/H/K, T87S/I, G88A/S/T, Y89F, H90N/Q/K, G91A/S/T, T94N/D/A/M/V/I, R95K/Q,

D96N/V/Q/I, F97Y, I174N/Q/L, S175T/A/N/D, N176S/T/H/Q/P, D178N/Q/E/K/H, D179Y/N/H, R180W, Y181R/F/C/L, E182D, A183S/C/G, Q184E, K186R, N187Q/E/L/F/H/K/V/L, F188Y/L/I/H/N, T189N/D/A/S/H/Y/G, D190E/Q/H/N/K, A192T/D/E/N/K, G193A/S/T, F194Y, S195N/D/E/R/K/G, L196I. See the specification at page 7, lines 14-28.

(3) A maltogenic alpha-amylase having one or more following positions altered in SEQ ID NO: 2: D17, A30, S32, R95, H103, N131, Q201, I174, H169, V74, L75, L78, T80, L81, T87, G88, Y89, H90, G91, T94, R95, D96, F97, Y167, F168, H169, H170, N171, G172, D173, I174, S175, N176, D178, D179, R180, Y181, E182, A183, Q184, K186, N187, F188, T189. See the specification at page 7, line 35 to page 8, line 2.

(4) A maltogenic alpha-amylase having an alteration of the partial sequence N28-P29-A30-K31-S32-Y33-G34 of SEQ ID NO: 2. See the specification at page 8, lines 4-9.

(5) A maltogenic alpha-amylase having one or more of the following substitutions in SEQ ID NO: 2: D17E/Q, A30M/L/A/V/I/E/Q, S32D/E/N/Q, R95M/L/A/V/I/E/Q, H103Y/N/Q/D/E, N131D, Q201E, I174E/Q, H169N/D/E/Q, V74I, L75N/D/Q/I/V, L78N/I, T80I/L/V/S/N/G, L81I/V/S/T/N/Q/K/H, T87S/I, G88A/S/T, Y89F, H90N/Q/K, G91A/S/T, T94N/D/A/M/V/I, R95K/Q, D96N/V/Q/I, F97Y, Y167F/R/C, F168Y, H169N/Q/K, H170N/Q/K, N171D/E/Q/H/R/K/G, G172A/T/S, D173N/S/T/Y/R/G, I174N/Q/L, S175T/A/N/D, N176S/T/H/Q/P, D178N/Q/E/K/H, D179Y/N/H, R180W, Y181R/F/C/L, E182D, A183S/C/G, Q184E, K186R, N187Q/E/L/F/H/K/V/L, F188Y/L/I/H/N, T189N/D/A/S/H/Y/G. See the specification at page 8, lines 15-23.

(6) A maltogenic alpha-amylase having one or more of the following positions altered in SEQ ID NO: 2: L51, L75, L78, G88, G91, T94, V114, I125, V126, T134, G157, L217, S235, G236, V254, V279, V281, L286, V289, I290, V308, L321, I325, D326, L343, F349, S353, I359, I405, L448, Q449, L452, I470, G509, V515, S583, G625, L627, L628, A670, L71, S72, V74, L75, L78, T80, L81, G83, T84, D85, N86, T87, G88, Y89, H90, G91, T94, R95, D96, F97, Y167, F168, H169, H170, N171, G172, D173, I174, S175, N176, D178, D179, R180, Y181, E182, A183, Q184, K186, N187, F188, T189, D190,

A192, G193, F194, S195, L196. See the specification at page 8, line 31 to page 9, line 9.

(7) A maltogenic alpha-amylase having one or more of the following substitutions in SEQ ID NO: 2: L217 in combination with L75 (e.g. L217F/Y in combination with L75F/Y), L51W, L75F/Y, L78I, G88A/V/T, G91T/S/V/N, T94V/I/L, V114V/I/L, I125L/M/F/Y/W, V126I/L, T134V/I/L/M/F/Y/W, G157A/V/I/L, L217V/I/M/F/Y/W, S235I/L/M/F/Y/W, G236A/V/I/L/M/F/Y/W, V254I/L/M/F/Y/W, V279M/I/L/F, V281I/L/M/F/Y/W, L286F, V289I/L/R, I290M/L/F, V308I/L/M/F/Y/W, L321I/M/F/Y/W, I325L/M/F/Y/W, D326E/Q, L343M/F/Y/W, F349W/Y, S353V/I/L, I359L/M/F/Y/W, I405M/L/Y/F/W, L448Y, Q449Y, L452M/Y/F/W, I470M/L/F, G509A/V/I/L/M/S/T/D/N, V515I/L, S583V/I/L/V, G625A/V/I/L/M/F/Y/W, L627M/F/Y, L628M/I/F/Y/W and A670V/I/L/M/F/Y/W, L71I, S72C, V74I, L75N/D/Q/I/V, L78N/I, T80I/L/V/S/N/G, L81I/V/S/T/N/Q/K/H, G83A/S/T/N/Q/E/D/R/H/L, T84S/A/N/D/G, D85A/T/S/N/G, N86Q/E/D/Y/H/K, T87S/I, G88A/S/T, Y89F, H90N/Q/K, G91A/S/T, T94N/D/A/M/V/I, R95K/Q, D96N/V/Q/I, F97Y, Y167F/R/C, F168Y, H169N/Q/K, H170N/Q/K, N171D/E/Q/H/R/K/G, G172A/T/S, D173N/S/T/Y/R/G, I174N/Q/L, S175T/A/N/D, N176S/T/H/Q/P, D178N/Q/E/K/H, D179Y/N/H, R180W, Y181R/F/C/L, E182D, A183S/C/G, Q184E, K186R, N187Q/E/L/F/H/K/V/L, F188Y/L/I/H/N, T189N/D/A/S/H/Y/G, D190E/Q/H/N/K, A192T/D/E/N/K, G193A/S/T, F194Y, S195N/D/E/R/K/G, L196I. See the specification at page 9, lines 4-26.

(8) A maltogenic alpha-amylase having a modification in position V281 and/or A629 of SEQ ID NO:2, including a maltogenic alpha-amylase having a modification of V281Q and/or A629N/D/E/Q in SEQ ID NO:2. See the specification at page 9, line 28-34.

(9) A maltogenic alpha-amylase having a modification at one or more positions in SEQ ID NO: 2: A30, K40, N115, T142, F188, T189, P191, A192, G193, F194, S195, D261, N327, K425, K520 and N595. See the specification at page 10, lines 3-5.

(10) A maltogenic alpha-amylase having one or more of the following substations or deletions in SEQ ID NO: 2: A30D, K40R, N115D, T142A, F188L, T189Y, Δ (191-195), D261G, D261G, N327S, K425E, K520R and N595I. See the specification at page 10, lines 5-9.

(11) A maltogenic alpha-amylase having one or more of the following substations or deletions in SEQ IND NO:2: 192-A-193; Δ (191-195); D17E; S32Q; S32D; S32N; H103Y; N131D; I174Q; I174E; N176S; F188H; F188E; Δ 191; 192-A-193; 192-A-G-193; Δ 192; Δ 262-266; F284E; F284D; F284K; T288K; T288R; N327D; G397P;N115D+ F188L; T142A+ D261G; G370N+ N371G; N115D+ F188L; A30D+ K40R+ D261G; F188L+ V336L+ T525A; F188I+ Y422F+ I660V; F188L+ D261G+ T288P; Δ (191-195)+ F188L+ T189Y; K40R+ F188L+ D261G+ A483T; T142A+ N327S+ K425E+ K520R+ N595I;T142A+ N327S+ K425E+ K520R+ N595I. See the specification at page 10, lines 14-17.

The above maltogenic alpha-amylases, including how to obtain nucleic acid sequences encoding these sequences, are also described in WO 99/43794 (see, e.g., at page 21-26 and Example 1), which is referenced in the present specification for disclosing suitable maltogenic alpha-amylases. See the specification at page 6. WO 99/15636 also discloses comparative testing that was made between a number of maltogenic alpha-amylases. See Examples 2-8 of WO 99/15636. Although many more maltogenic alpha-amylase variants were actually made and tested, as stated in the Declaration of Joel Cherry, WO 99/15636 specifically describes the comparative testing that was carried out with following maltogenic alpha-amylases:

(1) SEQ ID NO:2 having the alteration of F188H;
(2) SEQ ID NO:2 having the alteration of F188E;
(3) SEQ ID NO:2 having the alteration of T288R;
(4) SEQ ID NO:2 having the alteration of N327D;
(5) SEQ ID NO:2 having the alteration of N131D;
(6) SEQ ID NO:2 having the alteration of I174Q;
(7) SEQ ID NO:2 having the alteration of G397P;
(8) SEQ ID NO:2 having the alteration of H103Y;
(9) SEQ ID NO:2 having the alteration of S32Q;
(10) SEQ ID NO:2 having the alteration of S32D;
(11) SEQ ID NO:2 having the alteration of S32N;
(12) SEQ ID NO:2 having the alteration of N176S;
(13) SEQ ID NO:2 having the alteration of D17E;
(14) SEQ ID NO:2 having the alteration of I174E;
(15) SEQ ID NO:2 having the alteration of T288K;
(16) SEQ ID NO:2 having the alteration of Δ 191;

(17) SEQ ID NO:2 having the alteration of Δ 192;

(18) SEQ ID NO:2 having the alteration of Δ (191-195);

(19) SEQ ID NO:2 having the alteration of Δ 262-266;

(20) SEQ ID NO:2 having the alteration of 192-A-193;

(21) SEQ ID NO:2 having the alteration of 192-A-G-193;

(22) SEQ ID NO:2 having the alteration of T142A + D261G +T288P +Q449R;

(23) SEQ ID NO:2 having the alteration of T142A+ D261G;

(24) SEQ ID NO:2 having the alteration of T142A+ N327S+ K425E+ K520R+ N595I;

(25) SEQ ID NO:2 having the alteration of G370N+ N371G;

(26) SEQ ID NO:2 having the alteration of F188L + D261G + T288P;

(27) SEQ ID NO:2 having the alteration of F188L+ V336L+ T525A;

(28) SEQ ID NO:2 having the alteration of F188I+ Y422F+ I660V;

(29) SEQ ID NO:2 having the alteration of F188L + D261G + T288P + A483T;

(30) SEQ ID NO:2 having the alteration of A197P + D261G + T288P + N342S;

(31) SEQ ID NO:2 having the alteration of A30D+ K40R+ D261G;

(32) SEQ ID NO:2 having the alteration of K40R+ F188L+ D261G+ A483T;

(33) SEQ ID NO:2 having the alteration of N115D+ F188L;

(34) SEQ ID NO:2 having the alteration of N26S + F188L + D261G + T288P + T594A + I600V; and

(35) SEQ ID NO:2 having the alteration of N26S + T80A + F188L + D261G + T288P + R291L

See Examples 2-8.

Thus, contrary to the Examiner's allegations, numerous species of maltogenic alpha-amylase are disclosed in the present specification and in the public domain and were possessed by Applicants. Indeed, the U.S. Patent Office has already determined that Applicants were in possession of such a genus of representative species, as evidence by the issuance of U.S. Patent No. 6,162,628.

The Examiner has rejected the above evidence of representative species of the genus on the basis that (1) the representative species of the genus are defined in the specification and in WO 99/15636 only by their protein sequence as compared to the nucleic acid sequence and the claims require the use of nucleic acids not proteins (see the Examiner's allegations in the Office action of November 14, 2003 at the paragraph traversing page 3 and 4); (2) there is no guidance as to which combinations of the vast myriad of amino acid substitutions cited in the specification and in WO 99/15636 would recover maltogenic alpha-amylase activity (see the Office action of November 14, 2003 at the paragraph traversing page 3 and 4, se also the Advisory Action); and (3)

there is no teaching of conserved sequences of the genes which are correlated with function (see the Office action of November 14, 2003 at the paragraph traversing page 3 and 4). As discussed below, each of the Examiner's grounds for rejecting this evidence are in clear error.

First, the Examiner's assertion that a description of the examples of maltogenic alpha-amylases by their protein sequence rather than the encoding nucleic acids is not sufficient to show possession of a genus of nucleic acids encoding the maltogenic alpha-amylase is incorrect as it fails to consider, among other things, both the teachings of the specification and the level of skill in the art. In particular, although the specification describes maltogenic alpha-amylases by their protein sequence, it is well recognized in the art that the nucleic acid sequences encoding such amino acids sequences are known because the genetic code is widely known and, moreover, such nucleic acids can be readily prepared from such information by using standard methods known in the art for preparing nucleic acids encoding a known protein sequence. For example, the specification of the instant application at page 13, specifically teaches:

> Alternative, the DNA sequence encoding the enzyme may be prepared synthetically by established standard methods, e.g., the phosphoroamidite method described by S.L. Beaucage and M.H. Caruthers (1981) or the method described by Matthes et al. (1984). In the phosporoamidite method, oligonucleotides are synthesized, e.g., in an automatic DNA synthesizer, purified, annealed, ligated and cloned in appropriate vectors.

In this regard, Applicants are not required to disclose the nucleic acid sequence information because such sequence information is readily obtained from the information already provided in the specification or provided in the public domain in WO 99/43794. That is, Applicants simply choose in the patent application to describe the nucleic acid sequences encoding maltogenic alpha-amylases by providing the nucleic acid and protein sequence of a reference sequence (SEQ ID NO:1 and SEQ ID NO:2, respectively) and then by describing the amino acids changes relative to the reference amino acid sequence. However, the fact that Applicants did not recite the encoding nucleic acids of the variants does not mean that an artisan would conclude that Applicants did not possess such nucleic acids. To the contrary, a description of specific amino acid changes to a reference protein that is described by both the amino acid sequence and nucleic acid sequence is unquestionably possession of both the protein of such sequences and the nucleic acids encoding such sequences.

Moreover, although the Examiner has completely dismissed the Declaration of Dr. Joel Cherry (submitted by Applicants in the Amendment of May 3, 2004), as entirely an "opinion," Dr. Cherry's declaration is certainly not an unsubstantiated opinion lacking scientific credibility. Dr.

Cherry's declaration, although factually unnecessary, was submitted to further support that Applicants' description of the maltogenic alpha-amylase variants by the protein sequences was a sufficient description of the nucleic acid sequences and that Applicants were in possession of numerous species of nucleic acids encoding maltogenic alpha-amylases. Specifically, Dr. Joel Cherry submitted a declaration attesting to the facts behind the work that was done in preparing the maltogenic alpha-amylase variants described in the specification of the instant application and in WO 99/43794. In particular, Dr. Cherry states that the work involved producing nucleic acids encoding the maltogenic alpha-amylase variants disclosed, expressing the genes encoding the maltogenic alpha-amylase variants, and testing many of the maltogenic alpha-amylase variants in various assays. (See Cherry Declaration at paragraphs 5 and 6, describing that the work entailed producing thousands of new maltogenic alpha-amylases variants).

The Cherry Declaration does contain an opinion in that Dr. Cherry concludes that the skilled artisan is able to produce nucleic acids encoding the maltogenic alpha-amylase variants based on the disclosure of the amino acid sequence of the variants of a reference sequence when combined with a description of the nucleic acid sequence and protein sequence of the reference sequence, as such skills were routine in the art at the time of the filing of the application. However, Dr. Cherry's opinion is based on both his considerable expertise and his actual work in preparing the maltogenic alpha-amylase variants described in WO 99/43794. It is unclear how the Examiner can disagree with this opinion from a scientific standpoint, and how it can be dismissed as merely an "opinion."

Moreover, Applicants' assertion as to possession of the nucleic acids encoding the described maltogenic alpha-amylase proteins and Dr. Cherry's agreement is actually a conclusion stated in the Patent Office's Written Description Guidelines. In particular, Footnote 57 of the Patent Office's Written Description Guidelines, states that

> [I]n molecular biology art, **if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence.** Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species.

Therefore, the Examiner's assertion that the description of the amino acid sequence of the maltogenic alpha-amylases by their protein structure is not evidence of possession of the nucleic acid sequence is clearly erroneous.

The Examiner also improperly justifies the written description requirement rejection on the ground that the specification does not provide guidance as to which combinations of the

"vast myriad of amino acid substitutions cited in the specification would recover maltogenic alpha-amylase activity." Foremost, the Examiner has not provided any evidence or reasons as to why an artisan would need a description of all of the possible combinations of the vast myriad of alterations disclosed in the specification and which ones retain maltogenic alpha-amylase in order for the artisan to conclude that applicants were in possession of the claimed invention. The claims are not claiming variants of SEQ ID NO:2, and the production of variants is not an element of the claims. In fact, the term variant doesn't appear in any claim. The written description requirement addresses the claimed subject matter, and in this regard, the claims are directed to transgenic cells, seeds and plants having nucleic acids encoding maltogenic alpha-amylases having at least 70% identity to SEQ ID NO:2. Accordingly, the claims do not require that the artisan make all of the possible combinations of the vast myriad of amino acid substitutions recited in the specification for SEQ ID NO:2 and test to see if they retain maltogenic alpha-amylase activity. Thus, it is not clear why guidance as to the which combinations of the "vast myriad" of the disclosed alterations of SEQ ID NO:2 is relevant to whether the claimed invention of transgenic cereal plants, seeds and cells comprising a nucleic acid sequence encoding a maltogenic alpha-amylase has adequate written description support in the specification.

The variants of SEQ ID NO:2 which Applicants reference in the specification and in the cited patent publication are provided in the specification as examples of preferred maltogenic alpha-amylases and evidence possession of numerous maltogenic alpha-amylases, and thus, evidence of a possession of a genus of nucleic acids encoding maltogenic alpha-amylases for use in the claimed invention. With respect to additional alpha-amylase falling within the scope of the recitation of nucleic acids encoding maltogenic alpha-amylases having at least 70% identity to SEQ ID NO:2, Applicants are certainly not required under the written description requirement to disclose all of the various possible combinations of alterations and whether such combinations retain maltogenic alpha-amylase activity in order to show that Applicants possess a genus of nucleic acids encoding maltogenic alpha-amylase. Applicants are only required to provide sufficient information for the artisan to conclude that Applicants were in possession of the claimed invention.

Moreover, the claimed invention need not be described in *haec verba* to satisfy the description requirement as the relevant analysis is whether the claim limitations were described so that one of skill in the art would recognize that the applicants had invented the claimed subject matter. As discussed above, Applicants have met this showing by a recitation of a structural feature which is common to the members of the genus, and which distinguishes the

genus from other subject matter, and/or by a recitation of a representative number of nucleic acid falling within the scope of the genus. Thus, additional information on additional combination of vast myriad of the disclosed substitutions of SEQ ID NO:2 that the Examiner is curious about has no bearing on whether the written description requirement has been satisfied.

Notwithstanding the above, although the information on the additional combinations of vast myriad of substitutions disclosed is not believed to be necessary for an artisan to conclude that Applicants had invented the claimed transgenic cereal plants, cereal plant cells and cereal plant seeds, an artisan could nevertheless obtain such information based on the information provided in the specification and in the public domain. In particular, the specification and WO 99/15636 provide sufficient guidance for the artisan, if desirable, to prepare additional combinations of the vast myriad of substitutions disclosed for SEQ ID NO:2 and test whether they have the desired functional activity. In particular, an artisan simply needs to prepare combinations of the disclosed substitutions and test whether they have the desired functional activity carrying out the assays described in the specification and in the public domain (e.g., WO 99/15636).

Moreover, contrary to the Examiner's allegation, WO 99/15636 provides a description of residues which are important to the overall structure of maltogenic alpha-amylases and to important areas of the maltogenic alpha-amylase. In particular, WO 99/15636 provides the three dimensional structure of the maltogenic alpha-amylase of SEQ ID NO:2, which is representative of the genus. WO 99/15636 also specifically describes important conserved sequences/structures of maltogenic alpha-amylases, including, identifying the domains of the maltogenic alpha-amylases, and which amino acids make up the domains (see col. 4, lines 40-48); identifying where the active site residues are located, and identifying which residues which make up the active site (see col. 4, lines 50-67), identifying the number and location of the calcium ions (see col. 5, lines 33-35), and identifying the residues which are involved in substrate binding (see col. 5, lines 56 to col. 6, line 15).

Thus, the specification and WO 99/15636 also provide detailed guidance of both conserved sequences, sequence which are important for function, and sequences which can be altered without disrupting maltogenic alpha-amylase activity, as well as detailed information of the ways in which the protein's structure relates to its function. This teaching, coupled with numerous examples and the ability to test for functional mutants with the assays provided in the specification or the public domain (e.g., WO 99/15636) sufficiently describe how to make a vast myriad of additional variants of SEQ ID NO:2, assuming that such information was even relevant to establish written description support for the claimed invention.

Therefore, the Examiner's grounds do not establish why one of ordinary skill in the art would be unable to recognize that Applicants were in possession of transgenic cereal plants, cereal plant cells and cereal plant seeds comprising nucleic acid sequence encoding maltogenic alpha-amylase having at least 70% identity to amino acids 34-719 of SEQ ID NO:2.

In sum, Applicants' specification provides a precise definition by structure of the genus of materials sufficient to distinguish it from other materials and (2) a description of the genus by recitation of a representative number of species falling within the scope of the genus. See, e.g., *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997); *Enzo Biochem v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002. In particular, Applicants' specification provides a recitation of structural features which are common to the members of the recited nucleic acid sequences as applicants have defined this genus by the art recognized, and reliable structural feature of percent identity of the amino acid sequences encoded by the genes. Applicants have also provided a recitation of numerous representative members falling within the scope of the genus, including, the numerous variants described in the application, which are also described in WO 99/43794. With respect to preparing the transgenic plants, cells and seeds, Applicants have provided a very detailed description of how to transform cereal plant cells, cereal plant seeds and cereal plants using the maltogenic alpha-amylase genes described. In particular, the specification teaches how to prepare an appropriate expression construct and how to transform a plant cell to prepare a transgenic plant and plant seed. See the specification at page 14 to page 17. Further detailed guidance is provided in the Examples. In particular, Example 1 provides guidance on how to prepare a plasmid, how to transform a wheat plan, and how to verify the preparation of the transgenic wheat plant. Example 2 provides guidance for regeneration of a wheat plant from wheat protoplast cells.

Accordingly, based on the disclosure provided in the specification, the written description requirement is satisfied as the description provides sufficient information to establish that Applicants invented transgenic cereal plants, cereal plant cells and cereal plant seeds comprising nucleic acid sequence encoding maltogenic alpha-amylase having at least 70% identity to amino acids 34-719 of SEQ ID NO:2. Applicants therefore respectfully submit that the rejection of claims 23-25 and 27-37 as lacking written description support is improper and should be reversed.

B. Claims 23-25 and 27-37 Are Enabled

1. The Enablement Rejection

Claims 23-37 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement. The enablement rejection initially focused on both the genus of nucleic acids encoding maltogenic alpha-amylase and the sub-genus of nucleic acids encoding maltogenic alpha-amylases having 70% sequence identity to SEQ ID NO:2. Although Applicants maintain that the genus of maltogenic alpha-amylases is adequately described in the specification so as to enable one skilled in the art to practice the claimed invention as to maltogenic alpha-amylase in general, to expedite prosecution, the claims were amended during prosecution to recite that the "nucleotide sequence encodes a maltogenic alpha-amylase having at least 70% identity to amino acids 34-719 of SEQ ID NO:2."

In the first Office Action, the Examiner asserted that claims lacked enablement, as follows:

> Given the lack of guidance for isolating any maltogenic alpha-amylase gene, or for making functional maltogenic alpha-amylases with any number of amino acid substitutions; or for making any non-exemplified polynucleotide having 70% sequence identity to SEQ ID NO:1, the breadth of the claims and given the unpredictability in the art, under trial and error experimentation would be needed by one skilled in the art to isolate a multitude of non-exemplified maltogenic alpha-amylase, or to evaluate the ability of a multitude of non-exemplified functional maltogenic variants or non-exemplified polynucleotide sequences having at least 70% sequence identity to alter the delay of staling of bread baked from the seeds of any of the claimed non-exemplified transformed cereal plant species.

See the Office Action of Office Action of April 11, 2003 at page. 7.

The Examiner further asserted that

> Applicant teach SEQ ID NO:1 and 2; hypothetical amino acid substitutions to the polypeptide of SEQ ID NO:2 from maltogenic alpha-amylase variants disclosed in WO 99/43794, and prophetic biolistic transformation of wheat; and a proposed construction of a construct comprising the "Novamyl" (SEQ ID NO:1) maltogenic alpha-amylase transformed into wheat protoplast cells and regenerated into mature wheat plants.

See the Office Action of April 11, 2003 at page 4.

The Examiner also cited *Fourgoux-Nicol et al,*. Plant Molecular Biology, 40:857-872 (1999), *Bround P. et al.*, Science Vol. 282, 13 (1998), *Guinto, E. R., et al.*, PNAS, Vol.. 96, pp. 1852-1857 (1999), Nielsen J. Prot. Eng., Vol. 14, No. 7, pp 505-512 (2001), and *Sweetlove, et*

al., Biochem. Vol. 320, pp. 493-398 as allegedly exemplifying the unpredictability in obtaining genes encoding functional proteins in general and transforming a plant in general.

In Applicants' response of August 19, 2003, Applicants pointed out the claimed invention is claiming transgenic cereal plants, not maltogenic alpha-amylase variants of SEQ ID NO:2, and that the specification discloses how to prepare such transgenic plants by cloning a DNA sequence encoding a maltogenic alpha-amylase, preparing an expression construct, selecting suitable plant species and transforming the plant. Applicants pointed out that the Examiner has misinterpreted the Sweetlove reference as showing unpredictability of making transgenic plants, when, in fact, Sweetlove was a successful experiment as they were able to transform plant cells to increase the activity of an enzyme. Applicants also noted that any experiment required to practice the claimed invention would not be undue, but would involve routine experimentation normally encountered and performed when preparing transgenic organisms.

In the Final Office action, the Examiner alleged that "Applicant has not described the claimed sequences of the invention...., Applicant has not taught how to make the broadly claimed sequences of the invention and the host cells and plants therewith." The Examiner also asserted that "[g]iven the lack of teaching of which amino acid substitutions comprising a variant having 70% sequence identity to SEQ ID NO:2 without any teaching as to which combination of substitutions could be predictably eliminated, one skill in the art would be required to test a myriad of variants of maltogenic activity of the broadly claimed genus having 70% sequence identity and thus the claims are not enabled." The Examiner did not disagree with Applicants assertion that Sweetlove supports the enablement of the claimed invention, rather the Examiner states that the "claimed amount of maltogenic alpha-amylase effective to delay staling of baked bread, requiring the claimed variants have maltogenic activity in a plant and not just their mere presence."

In response to the Final Office action, Applicants expedited prosecution by amending the claims to recite that the "nucleotide sequence encodes a maltogenic alpha-amylase having at least 70% identity to amino acids 34-719 of SEQ ID NO:2." This limitation was found in the dependent claims. Applicants also argued that an artisan is able to practice the claimed invention commensurate in scope with the claims as Applicants have provided the artisan numerous species of maltogenic alpha-amylase genes representative of the scope of the claims and the specification teaches how to prepare transgenic cereal plants, cereal plant cells and seeds comprising these genes. Applicants pointed out that it is not a requirement to describe each and every embodiment of the claimed invention and the Examiner has provided no

evidence or reasoning why an artisan would be unable to produce the claimed transgenic plants, cells and seeds. Applicants also submitted a declaration from one of the inventors of the cited patent publication WO 99/43794, who attests to the facts of the preparation of the maltogenic alpha-amylases.

In the Advisory Action, the Examiner concludes that Applicants have not enabled the artisan as to which combinations of the "vast myriad of amino acid substitutions cited in the specification would recover maltogenic alpha-amylase activity over the entire claimed scope of 70% sequence identity to amino acid residues 34-719 of SEQ ID NO:2." The Examiner also dismisses the Declaration of Dr. Joel Cherry as his "opinion" which does not rebut the evidence provided by the Examiner.

2. The Legal Standard

Section 112 of U.S. Patent Code requires that the specification be "enabling" to a person skilled in the art to which the invention pertains. "A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 USPQ at 369.

It is also well settled that an assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974). See also *U.S. v. Telectronics*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974); *Ex parte Hitzeman*, 9 U.S.P.Q.2d 1821 (BPAI 1988). In the absence of any evidence or apparent reason why compounds do not possess the disclosed utility, the allegation of utility in the specification must be accepted as correct. *In re Kamal*, 158 U.S.P.Q. 320 (C.C.P.A. 1968). See also *In re Stark*, 172 U.S.P.Q. 402, 406 n. 4 (C.C.P.A. 1972) (the burden is upon the Patent Office to set forth reasonable grounds in support of its contention that a claim reads on inoperable subject matter).

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As stated in *Wands*, [w]hether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *See id.* at 1404. The *Wands* factors which may be relevant for determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation

necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Id.*

3. Argument

The enablement rejection primarily focuses on whether the specification enables an artisan to make nucleic acid sequences encoding maltogenic alpha-amylase which have at least 70% identity to SEQ ID NO:2 for use in preparing the transgenic cells, seeds and plants. The Examiner alleges that because the specification does not have appropriate guidance for producing nucleic acids encoding maltogenic alpha-amylase having at least 70% identity to SEQ ID NO:2, that one of ordinary skill in the art would be reduced to undue experimentation. In the recent Advisory Action, the Examiner specifically concluded that Applicants have not enabled the artisan to which combinations of the "vast myriad of amino acid substitutions cited in the specification would recover maltogenic alpha-amylase activity over the entire claimed scope of 70% sequence identity to amino acid residues 34-719 of SEQ ID NO:2."

Enablement is based on the claimed invention. The claims are directed to the preparation of transgenic cereal plant cells, transgenic cereal plant seeds and transgenic cereal plants transformed with a nucleic acid encoding a maltogenic alpha-amylase which have at least 70% identity to amino acids 34-719 of SEQ ID NO:2. As discussed with regard to the standing written description rejection, the structural feature of 70% identity to a reference sequence inherently defines the function of the encoded products and provides a reasonable prediction of relatedness and the identification of members of the genus. In this regard, it is accepted in the art that nucleic acid sequences encoding polypeptides having 70% identity to a reference polypeptide will encode a polypeptide having a very similar function to the reference polypeptide.

Applicants' specification also provides numerous sources of maltogenic alpha-amylases that an artisan can use to practice the claimed invention, i.e., to prepare the claimed transgenic cereal plants, cereal plant cells and cereal plant seeds. In addition to the nucleic acid sequence of SEQ ID NO:1 encoding the maltogenic alpha-amylase of SEQ ID NO:2, the specification also, as previously discussed, provides numerous additional maltogenic alpha-amylases. In particular, an artisan can use nucleic acids encoding the following maltogenic alpha-amylase variants of SEQ ID NO:2:

(1) A maltogenic alpha-amylase having one or more of the following positions altered in SEQ ID NO:2: D127, V129, F188, A229, Y258, V281, F284, T288, N327, M330, G370, N371, D372, L71, S72, V74, L75, L78, T80, L81, G83,

T84, D85, N86, T87, G88, Y89, H90, G91, T94, R95, D96, F97, I174, S175, N176, D178, D179, R180, Y181, E182, A183, Q184, K186, N187, F188, T189, D190, A192, G193, F194, S195, L196. See the specification at page 7, lines 1-12.

(2) A maltogenic alpha-amylase having one or more of the following substitutions in SEQ ID NO:2: D127N/L, V129S/T/G/V, F188E/K/H, A229S/T/G/V, Y258E/D/K/R/F/N, V281L/T, F284K/H/D/E/Y, T288E/K/R, N327D, M330L/F/I/D/E/K, G370N, N371D/E/G/K, D372N/V, L71I, S72C, V74I, L75N/D/Q/I/V, L78N/I, T80I/L/V/S/N/G, L81I/V/S/T/N/Q/K/H, G83A/S/T/N/Q/E/D/R/H/L, T84S/A/N/D/G, D85A/T/S/N/G, N86Q/E/D/Y/H/K, T87S/I, G88A/S/T, Y89F, H90N/Q/K, G91A/S/T, T94N/D/A/M/V/I, R95K/Q, D96N/V/Q/I, F97Y, I174N/Q/L, S175T/A/N/D, N176S/T/H/Q/P, D178N/Q/E/K/H, D179Y/N/H, R180W, Y181R/F/C/L, E182D, A183S/C/G, Q184E, K186R, N187Q/E/L/F/H/K/V/L, F188Y/L/I/H/N, T189N/D/A/S/H/Y/G, D190E/Q/H/N/K, A192T/D/E/N/K, G193A/S/T, F194Y, S195N/D/E/R/K/G, L196I. See the specification at page 7, lines 14-28.

(3) A maltogenic alpha-amylase having one or more following positions altered in SEQ ID NO: 2: D17, A30, S32, R95, H103, N131, Q201, I174, H169, V74, L75, L78, T80, L81, T87, G88, Y89, H90, G91, T94, R95, D96, F97, Y167, F168, H169, H170, N171, G172, D173, I174, S175, N176, D178, D179, R180, Y181, E182, A183, Q184, K186, N187, F188, T189. See the specification at page 7, line 35 to page 8, line 2.

(4) A maltogenic alpha-amylase having an alteration of the partial sequence N28-P29-A30-K31-S32-Y33-G34 of SEQ ID NO: 2. See the specification at page 8, lines 4-9.

(5) A maltogenic alpha-amylase having one or more of the following substitutions in SEQ ID NO: 2: D17E/Q, A30M/L/A/V/I/E/Q, S32D/E/N/Q, R95M/L/A/V/I/E/Q, H103Y/N/Q/D/E, N131D, Q201E, I174E/Q, H169N/D/E/Q, V74I, L75N/D/Q/I/V, L78N/I, T80I/L/V/S/N/G, L81I/V/S/T/N/Q/K/H, T87S/I, G88A/S/T, Y89F, H90N/Q/K, G91A/S/T, T94N/D/A/M/V/I, R95K/Q, D96N/V/Q/I, F97Y, Y167F/R/C, F168Y, H169N/Q/K, H170N/Q/K, N171D/E/Q/H/R/K/G, G172A/T/S, D173N/S/T/Y/R/G, I174N/Q/L, S175T/A/N/D, N176S/T/H/Q/P, D178N/Q/E/K/H, D179Y/N/H, R180W, Y181R/F/C/L, E182D, A183S/C/G, Q184E, K186R, N187Q/E/L/F/H/K/V/L,

F188Y/L/I/H/N, T189N/D/A/S/H/Y/G.See the specification at page 8, lines 15-23.

(6) A maltogenic alpha-amylase having one or more of the following positions altered in SEQ ID NO: 2: L51, L75, L78, G88, G91, T94, V114, I125, V126, T134, G157, L217, S235, G236, V254, V279, V281, L286, V289, I290, V308, L321, I325, D326, L343, F349, S353, I359, I405, L448, Q449, L452, I470, G509, V515, S583, G625, L627, L628, A670, L71, S72, V74, L75, L78, T80, L81, G83, T84, D85, N86, T87, G88, Y89, H90, G91, T94, R95, D96, F97, Y167, F168, H169, H170, N171, G172, D173, I174, S175, N176, D178, D179, R180, Y181, E182, A183, Q184, K186, N187, F188, T189, D190, A192, G193, F194, S195, L196. See the specification at page 8, line 31 to page 9, line 9.

(7) A maltogenic alpha-amylase having one or more of the following substitutions in SEQ ID NO: 2: L217 in combination with L75 (e.g. L217F/Y in combination with L75F/Y), L51W, L75F/Y, L78I, G88A/V/T, G91T/S/V/N, T94V/I/L, V114V/I/L, I125L/M/F/Y/W, V126I/L, T134V/I/L/M/F/Y/W, G157A/V/I/L, L217V/I/M/F/Y/W, S235I/L/M/F/Y/W, G236A/V/I/L/M/F/Y/W, V254I/L/M/F/Y/W, V279M/I/L/F, V281I/L/M/F/Y/W, L286F, V289I/L/R, I290M/L/F, V308I/L/M/F/Y/W, L321I/M/F/Y/W, I325L/M/F/Y/W, D326E/Q, L343M/F/Y/W, F349W/Y, S353V/I/L, I359L/M/F/Y/W, I405M/L/Y/F/W, L448Y, Q449Y, L452M/Y/F/W, I470M/L/F, G509A/V/I/L/M/S/T/D/N, V515I/L, S583V/I/L/V, G625A/V/I/L/M/F/Y/W, L627M/F/Y, L628M/I/F/Y/W and A670V/I/L/M/F/Y/W, L71I, S72C, V74I, L75N/D/Q/I/V, L78N/I, T80I/L/V/S/N/G, L81I/V/S/T/N/Q/K/H, G83A/S/T/N/Q/E/D/R/H/L, T84S/A/N/D/G, D85A/T/S/N/G, N86Q/E/D/Y/H/K, T87S/I, G88A/S/T, Y89F, H90N/Q/K, G91A/S/T, T94N/D/A/M/V/I, R95K/Q, D96N/V/Q/I, F97Y, Y167F/R/C, F168Y, H169N/Q/K, H170N/Q/K, N171D/E/Q/H/R/K/G, G172A/T/S, D173N/S/T/Y/R/G, I174N/Q/L, S175T/A/N/D, N176S/T/H/Q/P, D178N/Q/E/K/H, D179Y/N/H, R180W, Y181R/F/C/L, E182D, A183S/C/G, Q184E, K186R, N187Q/E/L/F/H/K/V/L, F188Y/L/I/H/N, T189N/D/A/S/H/Y/G, D190E/Q/H/N/K, A192T/D/E/N/K, G193A/S/T, F194Y, S195N/D/E/R/K/G, L196I. See the specification at page 9, lines 4-26.

(8) A maltogenic alpha-amylase having a modification in position V281 and/or A629 of SEQ ID NO:2, including a maltogenic alpha-amylase having a

modification of V281Q and/or A629N/D/E/Q in SEQ ID NO:2. See the specification at page 9, line 28-34.

(9) A maltogenic alpha-amylase having a modification at one or more positions in SEQ ID NO: 2: A30, K40, N115, T142, F188, T189, P191, A192, G193, F194, S195, D261, N327, K425, K520 and N595. See the specification at page 10, lines 3-5.

(10) A maltogenic alpha-amylase having one or more of the following substations or deletions in SEQ ID NO: 2: A30D, K40R, N115D, T142A, F188L, T189Y, Δ (191-195), D261G, D261G, N327S, K425E, K520R and N595I. See the specification at page 10, lines 5-9.

(11) A maltogenic alpha-amylase having one or more of the following substations or deletions in SEQ IND NO:2: 192-A-193; Δ (191-195); D17E; S32Q; S32D; S32N; H103Y; N131D; I174Q; I174E; N176S; F188H; F188E; Δ 191; 192-A-193; 192-A-G-193; Δ 192; Δ 262-266; F284E; F284D; F284K; T288K; T288R; N327D; G397P;N115D+ F188L; T142A+ D261G; G370N+ N371G; N115D+ F188L; A30D+ K40R+ D261G; F188L+ V336L+ T525A; F188I+ Y422F+ I660V; F188L+ D261G+ T288P; Δ (191-195)+ F188L+ T189Y; K40R+ F188L+ D261G+ A483T; T142A+ N327S+ K425E+ K520R+ N595I;T142A+ N327S+ K425E+ K520R+ N595I. See the specification at page 10, lines 14-17.

An artisan is clearly enabled by the specification to obtain nucleic acids encoding the above variants, for example, by introducing these alterations in a nucleic acid sequence of SEQ ID NO:1 as the genetic code was widely known, and such sequence can be prepared, for example, as described in the specification at page 13:

> Alternative, the DNA sequence encoding the enzyme may be prepared synthetically by established standard methods, e.g., the phosphoroamidite method described by S.L. Beaucage and M.H. Caruthers (1981) or the method described by Matthes et al. (1984). In the phosporoamidite method, oligonucleotides are synthesized, e.g., in an automatic DNA synthesizer, purified, annealed, ligated and cloned in appropriate vectors.

Thus, the specification enables an artisan to obtain numerous maltogenic alpha-amylases having at least 70% identity to amino acids 34-719 of SEQ ID NO:2. Indeed, the U.S. Patent

Office has already determined that an artisan is enabled to prepare such maltogenic alpha-amylases, as evidence by the issuance of U.S. Patent No. 6,162,628.

The Examiner has also mischaracterized the maltogenic alpha-amylase described in the specification and WO 99/15636 (the '628 patent) as "hypothetical." See the Office Action of April 11, 2003. Although *some* of the alterations and combinations of alterations of SEQ ID NO:2 which are disclosed in the specification have not been made, many of the alterations have been made. Indeed, as stated by Dr. Cherry in his declaration, the co-inventor of the WO 99/15636, thousands of maltogenic alpha-amylase variants were produced which retained activity on starch. See the Cherry Declaration at page 3. For example, although certainly not an exhaustive list of all of the maltogenic alpha-amylase that were actually made by Applicants, WO 99/15636 specifically discloses the results of comparative testing of some embodiments. See Examples 2-8 of WO 99/15636. In particular, comparative testing is disclosed in WO 99/15636 for the following variants of SEQ ID NO:2, which are unquestionably not "hypothetical":

(1) SEQ ID NO:2 having the alteration of F188H;
(2) SEQ ID NO:2 having the alteration of F188E;
(3) SEQ ID NO:2 having the alteration of T288R;
(4) SEQ ID NO:2 having the alteration of N327D;
(5) SEQ ID NO:2 having the alteration of N131D;
(6) SEQ ID NO:2 having the alteration of I174Q;
(7) SEQ ID NO:2 having the alteration of G397P;
(8) SEQ ID NO:2 having the alteration of H103Y;
(9) SEQ ID NO:2 having the alteration of S32Q;
(10) SEQ ID NO:2 having the alteration of S32D;
(11) SEQ ID NO:2 having the alteration of S32N;
(12) SEQ ID NO:2 having the alteration of N176S;
(13) SEQ ID NO:2 having the alteration of D17E;
(14) SEQ ID NO:2 having the alteration of I174E;
(15) SEQ ID NO:2 having the alteration of T288K;
(16) SEQ ID NO:2 having the alteration of Δ 191;
(17) SEQ ID NO:2 having the alteration of Δ 192;
(18) SEQ ID NO:2 having the alteration of Δ (191-195);
(19) SEQ ID NO:2 having the alteration of Δ 262-266;
(20) SEQ ID NO:2 having the alteration of 192-A-193;
(21) SEQ ID NO:2 having the alteration of 192-A-G-193;
(22) SEQ ID NO:2 having the alteration of T142A + D261G +T288P +Q449R;

(23) SEQ ID NO:2 having the alteration of T142A+ D261G;

(24) SEQ ID NO:2 having the alteration of T142A+ N327S+ K425E+ K520R+ N595I;

(25) SEQ ID NO:2 having the alteration of G370N+ N371G;

(26) SEQ ID NO:2 having the alteration of F188L + D261G + T288P;

(27) SEQ ID NO:2 having the alteration of F188L+ V336L+ T525A;

(28) SEQ ID NO:2 having the alteration of F188I+ Y422F+ I660V;

(29) SEQ ID NO:2 having the alteration of F188L + D261G + T288P + A483T;

(30) SEQ ID NO:2 having the alteration of A197P + D261G + T288P + N342S;

(31) SEQ ID NO:2 having the alteration of A30D+ K40R+ D261G;

(32) SEQ ID NO:2 having the alteration of K40R+ F188L+ D261G+ A483T;

(33) SEQ ID NO:2 having the alteration of N115D+ F188L;

(34) SEQ ID NO:2 having the alteration of N26S + F188L + D261G + T288P + T594A + I600V; and

(35) SEQ ID NO:2 having the alteration of N26S + T80A + F188L + D261G + T288P + R291L

See Examples 2-8.

Thus, the Examiner's characterization of the alterations disclosed in the instant specification at page 7-11 as "hypothetical" is clear error.

The Examiner has also asserted, as set forth in the Advisory action, that the claims lack enablement because Applicants have not enabled the artisan as to which combinations of the "vast myriad of amino acid substitutions cited in the specification would recover maltogenic alpha-amylase activity over the entire claimed scope of 70% sequence identity to amino acid residues 34-719 of SEQ ID NO:2." As with the written description requirement, it is not clear why, for purposes of enablement, an artisan needs to know which additional combinations of the "vast myriad of amino acid substitutions cited in the specification would recover maltogenic alpha-amylase activity over the entire claimed scope of 70% sequence identity to amino acid residues 34-719 of SEQ ID NO:2." Enablement is directed to the claimed invention. The claims are not directed to making maltogenic alpha-amylases variants; rather, the claims are directed to transgenic cereal plant cells, transgenic cereal plant seeds, and transgenic cereal plants comprising a nucleic acid sequence encoding a maltogenic alpha-amylase having at least 70% identity to amino acids 34-719 of SEQ ID NO:2. In this regard, the claims do not require making all of the possible combinations of the recited alterations and test to see if they retain maltogenic alpha-amylase activity.

Moreover, the Examiner's conclusions fail to give appropriate consideration to the high level of skill in the art. As of the time of the invention, it was routine for persons of ordinary skill in the art to prepare and screen for variants of SEQ ID NO:1 which encode a protein that possess at least 70% identity to SEQ ID NO:2 and has maltogenic alpha-amylase activity. Indeed, as of March 1999, persons of ordinary skill in the art were able to routinely produce and screen in a very short period of time hundreds of thousands of mutants of a known sequence through mutagenesis and other techniques. Such technology available to the artisan at the time of the invention included localized and random mutagenesis protocols. This technology is referenced in the cited publication WO 99/15636, which evidences the skill in the art. See page 22-26. In addition, gene shuffling protocols of Stemmer, U.S. Patent No. 6,365,408, and other gene diversity protocols were also available to the artisan at the time of the invention and permit an artisan to rapidly generate virtually all of the possible variants of a sequence, and certainly, maltogenic alpha-amylase having at least 70% identity to SEQ ID NO:2.

As discussed with regard to the written description rejection, the information in the public domain also provides detailed guidance to assist an artisan when preparing such maltogenic alpha-amylases including detailed guidance of both conserved sequences, sequence which are important for function, and sequences which can be altered without disrupting maltogenic alpha-amylase activity, as well as detailed information of the ways in which the protein's structure relates to its function. In particular, WO 99/15636 provides a description of residues which are important to the overall structure of maltogenic alpha-amylases and to important areas of the maltogenic alpha-amylase. WO 99/15636 provides the three dimensional structure of the maltogenic alpha-amylase of SEQ ID NO:2, which is representative of the genus. WO 99/15636 also specifically describes important conserved sequences/structures of maltogenic alpha-amylases, including, identifying the domains of the maltogenic alpha-amylases, and which amino acids make up the domains (see col. 4, lines 40-48); identifying where the active site residues are located, and identifying which residues which make up the active site (see col. 4, lines 50-67), identifying the number and location of the calcium ions (see col. 5, lines 33-35), and identifying the residues which are involved in substrate binding (see col. 5, lines 56 to col. 6, line 15).

This teaching, coupled with numerous examples and the ability to test for functional mutants with the assays provided in the specification or the public domain (e.g., WO 99/15636) provide sufficient guidance to enable an artisan to make combinations of the vast myriad of substitutions disclosed for SEQ ID NO:2. Such work is certainly not undue, as the production of variants using this technology was routine in the art as of the filing of the application. Thus, although Applicants are not suggesting that one skilled in the art go out and make all of the

possible combinations of the alterations disclosed, and such information is not necessary to establish enablement of the claimed invention, the technology available to the artisan at the time of the invention nevertheless enabled the artisan to carry such tasks out.

Accordingly, the specification enables the artisan to obtain nucleic acids encoding maltogenic alpha-amylases required to practice the claimed invention. An artisan can then prepare a transgenic cereal plant cell, cereal plant seed or cereal plant by following the detailed guidance provided in the specification which provides a detailed description of how to transform cereal plant cells, cereal plant seeds and cereal plants using the maltogenic alpha-amylase genes. In particular, the specification describes how to prepare an appropriate expression construct and how to transform a plant cell to prepare a transgenic plant and plant seed. See the specification at page 14 to page 17. Further detailed guidance is provided in the examples, in particular, Example 1 provides guidance on how to prepare a plasmid, how to transform a wheat plant, and how to verify the preparation of the transgenic wheat plant. Example 2 provides guidance for regeneration of a wheat plant from wheat protoplast cells. It is also respectfully submitted that the state of the art as it relates to the transformation of plant cells, seeds and plants is very high as evidenced by the references cited in the specification, including WO 91/14772 (specification at page 1) and in the references discussed in the specification at page 15-17.

Accordingly, the specification enables the claimed invention because the specification contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter.

IX. CONCLUSION

For the foregoing reasons, Applicants submit that claims 23-25 and 27-37 are not unpatentable under 35 U.S.C. 112, for lack of written description and enablement. Accordingly, the final rejection of the claims should be reversed.

Respectfully submitted,

Date: July 22, 2004

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APPENDIX

Copy of Claims Involved in the Appeal

23. A transgenic cereal plant cell comprising a nucleotide sequence encoding a maltogenic alpha-amylase; wherein the maltogenic alpha-amylase has an amino acid sequence which has at least 70% identity to amino acids 34-719 of SEQ ID NO: 2.

24. The plant cell according to claim 23, wherein the plant cell is a wheat plant cell.

25. The plant cell according to claim 23, wherein the maltogenic alpha-amylase has the amino acid sequence of amino acids 34-719 of SEQ ID NO:2

27. The plant cell according to claim 23, wherein said wherein the nucleotide sequence is operably linked to a seed specific promoter.

28. The plant cell according to claim 23, wherein the nucleotide sequence encoding the maltogenic alpha-amylase is derived from a microorganism.

29. The plant cell according to claim 28, wherein the nucleotide sequence encoding the maltogenic alpha-amylase is derived from the *Bacillus* strain NCIB 11837.

30. A transgenic cereal plant regenerated from a plant cell of claim 23 or the progeny of the plant, wherein the plant and the progeny of the plant are capable of expressing maltogenic alpha-amylase in the seeds of the plant or the progeny of the plant.

31. A transgenic cereal plant comprising a nucleotide sequence encoding a maltogenic alpha-amylase; wherein the maltogenic alpha-amylase has an amino acid sequence which has at least 70% identity to amino acids 34-719 of SEQ ID NO: 2.

32. The plant according to claim 31 which is a wheat plant.

33. The plant according to claim 31, wherein the maltogenic amylase is a maltogenic alpha-amylase having the amino acid sequence of amino acids 34-719 of SEQ ID NO: 2.

34. A seed of the cereal plant of claim 31, wherein the seed includes maltogenic alpha-amylase in an amount effective to delay staling of bread baked from the seed.

35. A transgenic cereal seed comprising a maltogenic alpha-amylase in an amount effective to delay staling of bread baked from the seed; wherein the maltogenic alpha-amylase has an amino acid sequence which has at least 70% identity to amino acids 34-719 of SEQ ID NO: 2.

36. The seed of claim 34, wherein the maltogenic alpha-amylase is a maltogenic alpha-amylase having the amino acid sequence of amino acids 34-719 of SEQ ID NO: 2.

37. The seed of claim 36, wherein the seed is a wheat seed.